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GB-A- 2 127 689 **US-A- 4 675 189**

- **J CONTROLLED RELEASE, vol. 9, 1989, AMSTERDAM, THE NETHERLANDS, pages 111-122, XP000611562 MASAHARU ASANO ET AL: "IN VIVO CHARATERISTICS OF LOW MOLECULAR WEIGHT COPOLY(L-LACTIC ACID/GLYCOLIC ACID) FORMULATIONS WITH CONTROLLED RELEASE OF LUTEINIZING HORMONE-RELEASING HORMONE AGONIST"**
- **DATABASE WPI Section Ch, Week 8830 Derwent Publications Ltd., London, GB; Class A97, AN 88-210210 XP002019725 & JP-A-63 147 888 (ASAHI CHEMICAL IND KK) , 20 June 1988**

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Description

[0001] This invention relates to sustained release delivery systems, in particular poly(lactic/glycolic acid) (PLGA) delivery systems for the sustained release of therapeutic agents. In one aspect, this invention provides a sustained release composition comprising a PLGA matrix, a therapeutic agent, and a quaternary ammonium surfactant, in which the release profile of the therapeutic agent from the PLGA matrix is controlled by the concentration of the quaternary ammonium surfactant.

[0002] Poly(lactic/glycolic) acid (PLGA) refers to a copolymer of lactic acid (L) and glycolic acid (G), generally having a molecular weight up to about 50,000. Preferably, the ratio of L:G is at least 25:75. Additional comonomers and/or additives, such as plasticizers and stabilizers, may be present provided that such optional elements do not adversely impact upon the release of the therapeutic agent from the PLGA matrix.

[0003] Therapeutic agents include both large and small molecules intended for the treatment of acute or chronic conditions. The only limitation upon the agents is that they exhibit adequate efficacy for their intended use after incorporation into the PLGA matrix.

[0004] A quaternary ammonium surfactant is a salt of a nitrogenous cation in which a central nitrogen atom is bonded to four organic radicals and an anion, of general formula $R_4N^+X^-$ which exhibits surface active properties. Such materials may be categorized as detergents, wetting agents, or emulsifiers. In a quaternary ammonium surfactant generally at least one of the R groups is a long chain (greater than 6 carbon atoms) alkyl or aryl group.

Representative quaternary ammonium surfactants include, but are not limited to, those of the alkylammonium, benzalkonium, and pyridinium families. More specifically, the quaternary ammonium surfactants are selected from alkyltrimethylammonium salts, alkyldimethylbenzylammonium salts, and alkylpyridinium and imidazolium salts.

[0005] Sustained (or controlled) release refers to the gradual release of therapeutic agent from the PLGA matrix over a period of time. While there may be an initial burst phase, it is preferred that the release display relatively linear kinetics, thereby providing a constant supply of therapeutic agent over the release period. The release period may vary from several hours to several months, depending upon the therapeutic agent and its intended use. It is desirable that the cumulative release of the therapeutic agent from the matrix over the treatment period be relatively high to avoid the need for excessive loading of the matrix and consequent waste of unreleased therapeutic agent. The duration of the release period may be controlled by, *inter alia,* the mass and geometry of the matrix, the concentration of active agent, the locus of administration, the molecular weight and molar composition of the matrix, and, as demonstrated herein, the addition of release profile modifying agents.

[0006] The incorporation of the therapeutic agent and the release modifying agent into the PLGA matrix may be accomplished by any of various techniques known to the skilled artisan. Such techniques include the microencapsulation technologies disclosed in U.S. Patent Nos. 4,675,189 and 4,954,298, melt extrusion processes as exemplified herein, and melt pressing as described in *J. Controlled Release,* 9:111-122 (1989). The geometry of the matrix (e.g. cylinder, microsphere, fiber) will of course be dictated by the fabrication technique and will affect the concomitant release kinetics; however, it is expected that the current invention will be operable regardless of matrix geometry.

[0007] The concentration of therapeutic agent will vary depending upon the agent, its intended use, i.e. short or long duration, and the method of fabrication. In a preferred embodiment, the active agent concentration is from 0.1% to 20% by weight, more preferably from 1% to 10% by weight, most preferably from 2% to 6% by weight. The concentration of quaternary ammonium surfactant will also vary depending upon the agent, the matrix, the desired release profile, and the like. In a preferred embodiment the quaternary ammonium surfactant concentration is from 0.5% to 15% by weight, more preferably from 2% to 8% by weight.

[0008] To exemplify the invention three therapeutic agents of differing physical properties were examined: nafarelin acetate, a medium molecular weight, water-soluble peptide (MW = 1322), naproxen, a low molecular weight, water insoluble compound (MW = 230) and ketorolac tromethamine, a low molecular weight, water soluble compound (MW = 376). These therapeutic agents were melt blended with two representative quaternary ammonium surfactants: tetradecyldimethylbenzylammonium chloride (TDBAC) and cetylpyridinium chloride (CPC). Sodium chloride was used to prepare comparative, therapeutic agent-containing PLGA matrices.

[0009] Cylinders including the therapeutic agents (drugs) at a concentration of 4% by weight and the surfactants at various concentrations were prepared from PLGA's with weight-average molecular weights of 4,500 to 18,000 by the melt-extrusion method without the use of organic solvents.

[0010] PLGA's, with copolymer ratio of lactic acid/glycolic acid of 50/50 and weight-average molecular weights of 4,500, 10,000 and 18,000, respectively (abbreviated as PLGA-4,500, PLGA-10,000 and PLGA-18,000) were purchased from Taki Chemical Co., Ltd.; tetradecyldimethylbenzylammonium chloride (TDBAC), from Nippon Oil & Fats Co., Ltd.; and cetylpyridinium chloride (CPC), from Wako Pure Chemical Ind. Other chemicals were of reagent grade.

[0011] The molecular weight of PLGA was measured on a Shimadzu HPLC system (6A), columns: Waters ultrastyragel 10^2, 10^3 and 10^4 Å; mobile phase: THF; flow

rate: 1.0 ml/min.; wavelength: 230 nm; standard: polystyrene (Supelco Inc., molecular weight range of 760 - 90,000).

Example 1

[0012] This Example demonstrates that quaternary ammonium salts can modify the release profile of water soluble, medium molecular weight peptide drugs from PLGA matrices.

[0013] Cylinders containing 4% by weight nafarelin acetate (Syntex, Palo Alto, CA) in PLGA-4,500 without additive and with (by weight) 2% TDBAC, 4% TDBAC, 2% CPC, 4% CPC, 2% NaCl, or 20% NaCl were prepared as described below. A mixture (200 mg) of drug with PLGA and the selected amount of surfactant was placed in a glass tube and heated at a melt temperature of 75°C to melt the polymer. The melt was mixed homogeneously, charged into a polypropylene syringe and extruded. A cylinder 1.3 mm in diameter was obtained, cut into 5 mm lengths, and the drug content and the molecular weight of PLGA determined to confirm their stabilities during the preparation process, by high performance liquid chromatography (HPLC), as described below. The recovery of nafarelin from the cylinder was more than 90% and the molecular weight of the PLGA remained unaltered.

[0014] Nafarelin was extracted from the PLGA cylinder in a mixed solution of acetonitrile and potassium phosphate aqueous solution (23:77) and assayed by HPLC, column: Wakosil C8, 4.6 mm x 25 cm; mobile phase: 0.1 M $NH_4H_2PO_4$-CH_3CN (72:25:25); flow rate: 1.0 ml/min.; wavelength: 225 nm.

[0015] Drug release properties were studied at 37°C using a rotating bottle apparatus. A cylinder was put into a glass bottle containing 5 ml of 0.2M phosphate buffer, pH 7.0. The medium was replaced by a fresh one at specified times and analyzed for the released drug by HPLC under the same conditions as described above.

[0016] Fig. 1 shows the release profiles *in vitro* of nafarelin from the PLGA cylinders (MW = 4,500) with the different additives; (A): TDBAC, (B): CPC and (C): sodium chloride, respectively. Nafarelin release from the PLGA cylinder without additive was significantly sustained and followed the matrix release mechanism suggested by Higuchi (1963), i.e., the cumulative percentage of nafarelin released was proportional to the square root of time (correlation coefficient; r = 0.985). For 21 days in the release test, the total percentage of nafarelin released was limited to 42%. However, the nafarelin release from the PLGA cylinder with TDBAC or CPC as an additive was much more constant without leveling off for the entire test period and was accelerated depending on the amount of the additive used. The cylinders with TDBAC (2% and 4%) showed the complete release of nafarelin during 14 days. On the other hand, the percentage of nafarelin released from the cylinder with CPC (2%) was approximately 75% for 21 days. Since the molecular weights of TDBAC and CPC are similar (368 and 340, respectively), it appears that TDBAC surpasses CPC with regard to accelerating nafarelin release from PLGA matrices. The addition of sodium chloride (2% and 20%) to the PLGA cylinder did not significantly change the nafarelin release profile.

Example 2

[0017] This Example demonstrates that quaternary ammonium salts can modify the release profiles of low molecular weight, water insoluble drugs, from PLGA matrices.

[0018] Cylinders containing 4% by weight naproxen (Syntex, Palo Alto, CA) in PLGA-10,000 without additive and with (by weight) 2% TDBAC, 4% TDBAC, 4% NaCl, or 8% NaCl, were prepared as described below. A mixture (200 mg) of drug with PLGA and the selected amount of surfactant was placed in a glass tube and heated at a melt temperature of 80°C to melt the polymer. The melt was mixed homogeneously, charged into a polypropylene syringe and extruded. A cylinder 1.3 mm in diameter was obtained, cut into 5 mm lengths, and the drug content and the molecular weight of PLGA determined to confirm their stabilities during the preparation process, by high performance liquid chromatography (HPLC), as described below. The recovery of naproxen from the cylinder was more than 90% and the molecular weight of the PLGA remained unaltered.

[0019] Naproxen was extracted from the PLGA cylinder in a mixed solution of acetonitrile and potassium phosphate aqueous solution (23:77) and assayed by HPLC, column: Spherisorb C18, 4.6 mm x 25 cm; mobile phase: CH_3OH-H_2O-CH_3COOH (55:44:1); flow rate: 0.8 ml/min.; wavelength: 254 nm.

[0020] Drug release properties were studied at 37°C using a rotating bottle apparatus. A cylinder was put into a glass bottle containing 5 ml of 0.2M phosphate buffer, pH 7.0. The medium was replaced by a fresh one at specified times and analyzed for the released drug by HPLC under the same conditions as described above.

[0021] The release profiles of naproxen from the PLGA cylinders (MW = 10,000) with TDBAC and sodium chloride are shown in Figs. 2 (A) and (B), respectively. Naproxen release in excess of 90% from every cylinder illustrated in Fig. 2 was observed over 7 days. However, the naproxen release profile was affected by the additive used. Although an initial burst release of 64% of naproxen was seen for the PLGA cylinder without additive, by the addition of TDBAC at 2% and 4%, the PLGA cylinders showed complete and constant release of naproxen, independent of TDBAC content. While high initial burst release of naproxen was observed for the PLGA cylinders with sodium chloride (4% and 8%) also, the subsequent release was also accelerated and the total percentage of naproxen released over 4 days was about 90%. It is believed that the addition of sodium chloride increased the permeability of the PLGA matrices by

forming aqueous pores for the low molecular weight compound.

Example 3

[0022] This Example demonstrates that quaternary ammonium surfactants can modify the release profile of low molecular weight, water soluble drugs from PLGA matrices.

[0023] Cylinders containing 4% by weight ketorolac tromethamine (Syntex, Palo Alto, CA) in PLGA-18,000 without additive and with (by weight) 2% TDBAC, 4% TDBAC, 4% NaCl, or 8% NaCl were prepared as described below. A mixture (200 mg) of drug with PLGA and the selected amount of surfactant was placed in a glass tube and heated at a melt temperature of 95°C to melt the polymer. The melt was mixed homogeneously, charged into a polypropylene syringe and extruded. A cylinder 1.3 mm in diameter was obtained, cut into 5 mm lengths, and the drug content and the molecular weight of PLGA determined to confirm their stabilities during the preparation process, by high performance liquid chromatography (HPLC), as described below. The recovery of ketorolac from the cylinder was more than 90% and the molecular weight of the PLGA remained unaltered.

[0024] Ketorolac was extracted from the PLGA cylinder in a mixed solution of acetonitrile and potassium phosphate aqueous solution (23:77) and assayed by HPLC, column: Spherisorb C18, 4.6 mm x 25 cm; mobile phase: CH_3OH-H_2O-CH_3COOH (55:44:1); flow rate: 0.8 ml/min.; wavelength: 254 nm.

[0025] Drug release properties were studied at 37°C using a rotating bottle apparatus. A cylinder was put into a glass bottle containing 5 ml of 0.2M phosphate buffer, pH 7.0. The medium was replaced by a fresh one at specified times and analyzed for the released drug by HPLC under the same conditions as described above.

[0026] Fig. 3 illustrates the release profiles of ketorolac from the PLGA cylinders (MW = 18,000) with TDBAC and sodium chloride; (A): TDBAC and (B): sodium chloride, respectively. In spite of the low molecular weight and high solubility in water, a lag time with little drug release was shown for the PLGA cylinder without additive. After the lag time of 7 days, a rapid release of ketorolac was observed for the following 7 days and reached about 70%. In the cylinders with additive, while sodium chloride showed no effect on the ketorolac release, the lag time in the release profile decreased with increasing amounts of TDBAC and the release rates became more constant until the completion of the release. The results indicate that the high molecular weight (18,000) PLGA matrix was too dense for adequate penetration of water, but its permeability was improved by the addition of TDBAC.

Claims

1. A sustained release composition comprising a poly (lactic/glycolic) acid copolymer, a therapeutic agent, and a quaternary ammonium surfactant.

2. A composition of Claim 1 wherein the quaternary ammonium ion of said surfactant is selected from alkylammonium, benzalkonium, and pyridinium ions.

3. A composition of Claim 2 wherein the quaternary ammonium ion is selected from alkyltrimethylammonium, alkyldimethylbenzylammonium, and alkylpyridinium and alkylimidazolium ions.

4. A composition of Claim 3 wherein the quaternary ammonium ion is selected from tetradecyldimethylbenzylammonium and cetylpyridinium.

5. A composition of any one of Claims 1-4 wherein the molar ratio of lactic/glycolic acid in said poly(lactic/glycolic acid) polymer is at least 25:75.

6. A composition of any one of Claims 1-4 wherein said poly(lactic/glycolic acid) polymer has a weight average molecular weight of 4,500 to 50,000.

7. A composition of any one of Claims 1-4 wherein said poly(lactic/glycolic acid) polymer has a molecular weight of 4,500 to 18,000.

8. A composition of any one of Claims 1-7 wherein said quaternary ammonium surfactant comprises from 0.5 to 15 percent by weight of the composition.

9. A composition of any one of Claims 1-7 wherein said quaternary ammonium surfactant comprises from 2 to 8 percent by weight of the composition.

10. A composition of any one of Claims 1-9 wherein said therapeutic agent comprises from 0.1 to 20 percent by weight of the composition.

11. A composition of any one of Claims 1-9 wherein said therapeutic agent comprises from 1 to 10 percent by weight of the composition.

12. A composition of any one of Claims 1-9 wherein said therapeutic agent comprises from 2 to 6 percent by weight of the composition.

13. A composition of any one of Claims 1-12 wherein the therapeutic agent is selected from nafarelin, naproxen, and ketorolac.

Patentansprüche

1. Zusammensetzung, mit verzögerter Wirkstoffabgabe, umfassend ein Poly-(milch/glykol)-säure-Copolymer, einen Wirkstoff und ein oberflächenaktives Mittel auf der Basis eines quaternären Ammoniumions.

2. Zusammensetzung nach Anspruch 1, wobei das quaternäre Ammoniumion in dem oberflächenaktiven Mittel aus Alkylammonium-, Benzalkonium- oder Pyridiniumionen ausgewählt ist.

3. Zusammensetzung nach Anspruch 2, wobei das quaternäre Ammoniumion aus Alkyltrimethylammonium-, Alkyldimethylbenzylammonium-, Alkylpyridinium- und Alkylimidazoliumionen ausgewählt ist.

4. Zusammensetzung nach Anspruch 3, wobei das quaternäre Ammoniumion aus Tetradecyldimethylbenzylammonium- und Cetylpyridiniumionen ausgewählt ist.

5. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei das molare Verhältnis von Milch-/Glykolsäure in dem Poly-(milch/glykol)-säure-Copolymer mindestens 25:75 beträgt.

6. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei das Poly-(milch/glykol)-säure-Polymer ein durchschnittliches Molekulargewicht von 4 500 bis 50 000 hat.

7. Zusammensetzung nach einem der Ansprüche 1 bis 4, wobei das Poly-(milch/glykol)-säure-Polymer ein durchschnittliches Molekulargewicht von 4 500 bis 18 000 hat.

8. Zusammensetzung nach einem der Ansprüche 1 bis 7, wobei das oberflächenaktiven Mittel auf der Basis eines quaternären Ammoniumions von 0,5 bis 15 Gewichtsprozent der Zusammensetzung umfasst.

9. Zusammensetzung nach einem der Ansprüche 1 bis 7, wobei das oberflächenaktiven Mittel auf der Basis eines quaternären Ammoniumions von 2 bis 8 Gewichtsprozent der Zusammensetzung umfasst.

10. Zusammensetzung nach einem der Ansprüche 1 bis 9, wobei der Wirkstoff von 0,1 bis 20 Gewichtsprozent der Zusammensetzung umfasst.

11. Zusammensetzung nach einem der Ansprüche 1 bis 9, wobei der Wirkstoff von 1 bis 10 Gewichtsprozent der Zusammensetzung umfasst.

12. Zusammensetzung nach einem der Ansprüche 1 bis 9, wobei der Wirkstoff von 2 bis 6 Gewichtsprozent der Zusammensetzung umfasst.

13. Zusammensetzung nach einem der Ansprüche 1 bis 12, wobei der Wirkstoff aus Nafarelin, Naproxen und Ketorolac ausgewählt ist.

Revendications

1. Composition à libération prolongée comprenant un copolymère acide polylactique/acide polyglycolique, un agent thérapeutique et un agent tensioactif à base d'ammonium quaternaire.

2. Composition de la revendication 1 dans laquelle l'ion ammonium quaternaire dudit agent tensioactif est choisi parmi les ions alkylammonium, benzalconium et pyridinium.

3. Composition de la revendication 2 dans laquelle l'ion ammonium quaternaire est choisi parmi les ions alkyltriméthylammonium, alkyldiméthylbenzylammonium, alkylpyridinium et alkylimidazolium.

4. Composition de la revendication 3 dans laquelle l'ion ammonium quaternaire est choisi parmi les ions tétradécyldiméthylbenzylammonium et cétylpyridinium.

5. Composition de l'une quelconque des revendications 1 à 4 dans laquelle le rapport molaire de l'acide lactique à l'acide glycolique dans ledit polymère acide polylactique/acide polyglycolique est d'au moins 25:75.

6. Composition de l'une quelconque des revendications 1 à 4 dans laquelle ledit polymère acide polylactique/acide polyglycolique a un poids moléculaire moyen en poids de 4 500 à 50 000.

7. Composition de l'une quelconque des revendications 1 à 4 dans laquelle ledit polymère acide polylactique/acide polyglycolique a un poids moléculaire de 4 500 à 18 000.

8. Composition de l'une quelconque des revendications 1 à 7 dans laquelle ledit agent tensioactif à base d'ammonium quaternaire constitue de 0,5 à 15% en poids de la composition.

9. Composition de l'une quelconque des revendications 1 à 7 dans laquelle ledit agent tensioactif à base d'ammonium quaternaire constitue de 2 à 8% en poids de la composition.

10. Composition de l'une quelconque des revendica-

tions 1 à 9 dans laquelle ledit agent thérapeutique constitue de 0,1 à 20% en poids de la composition.

11. Composition de l'une quelconque des revendications 1 à 9 dans laquelle ledit agent thérapeutique constitue de 1 à 10% en poids de la composition.

12. Composition de l'une quelconque des revendications 1 à 9 dans laquelle ledit agent thérapeutique constitue de 2 à 6% en poids de la composition.

13. Composition de l'une quelconque des revendications 1 à 12 dans laquelle l'agent thérapeutique est choisi parmi la nafaréline, le naproxène et le kétorolac.

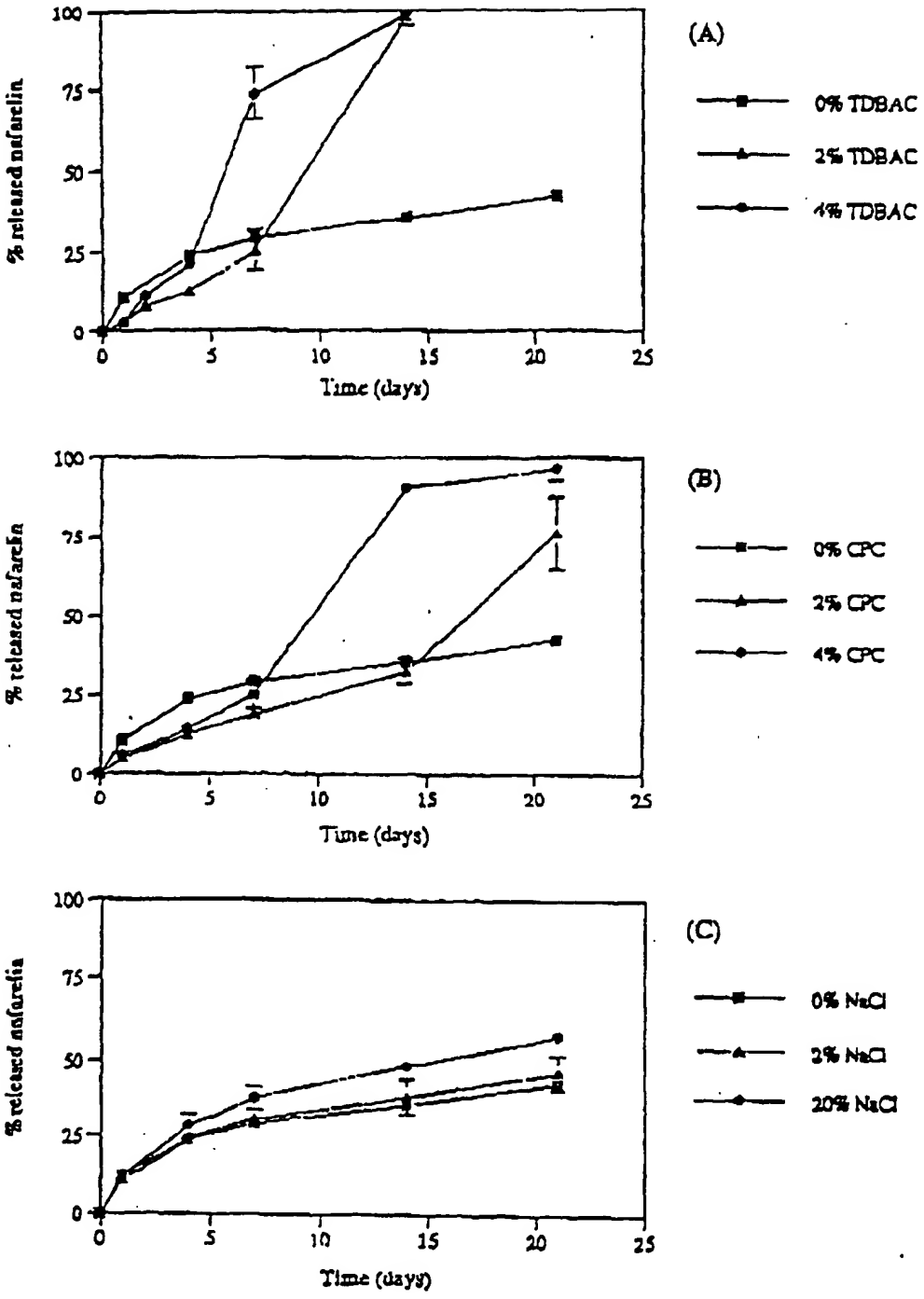

Fig. 1. Release profiles of nafarelin acetate from PLGA-4,500 cylinders containing different amounts of additives: (A) TDBAC; (B) CPC; (C) NaCl. Each value represents the mean±SD (n=3).

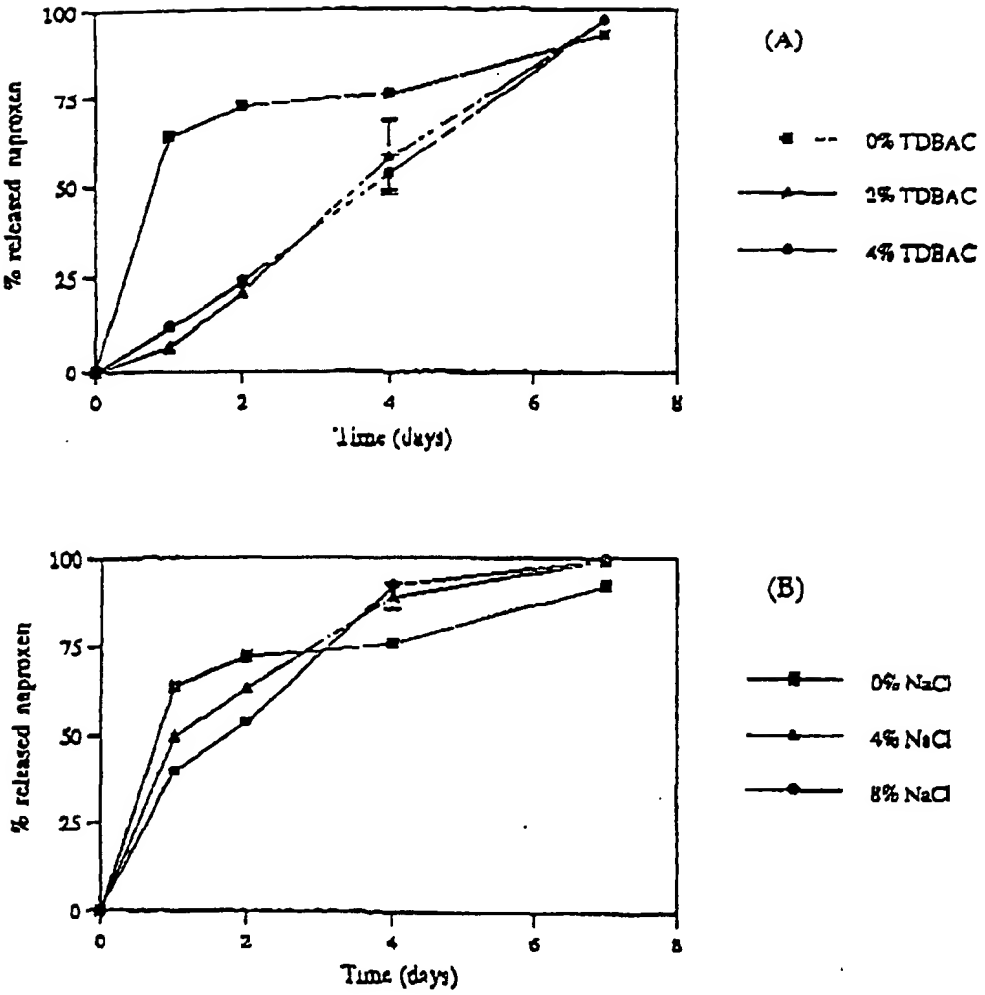

Fig.2. Release profiles of naproxen from PLGA-10,000 cylinders containing diffferent amounts of additives: (A) TDBAC; (B) NaCl. Each value represents the mean±SD (n=3).

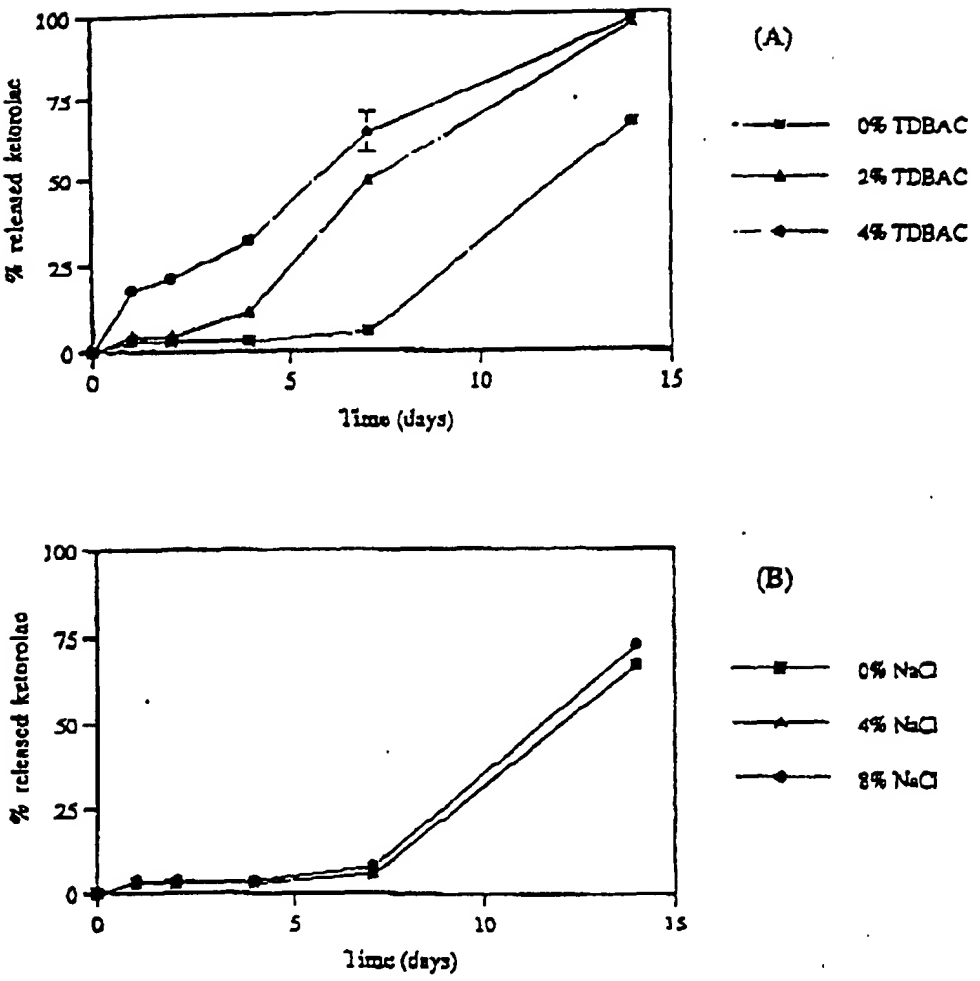

Fig.3. Release profiles of ketorolac tromethamine from PLGA-18,000 cylinders containing different amounts of additives: (A) TDBAC; (B) NaCl. Each value represents the mean±SD (n=3).